PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	Confirmation No. 9697
	)	Group Art Unit: 1648
Sallberg *et al.*	)	
	)	Examiner: A.M. Wehbe
Serial No. 09/466,035	)	
	)	
Filed: December 17, 1999	)	Atty. Dkt. No. PP1231.105 (002441.00249)

For: **METHODS OF NUCLEIC ACID IMMUNIZATION**

DECLARATION OF WILLIAM B KLIMSTRA UNDER 37 C.F.R. § 1.132

U.S. Patent and Trademark Office
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir:

I, William B. Klimstra, declare as follows:

1. I am an Associate Professor of Microbiology and Immunology with a Ph.D. in molecular virology and over 15 years experience studying the biology and immunology of alphaviruses and vaccine vectors derived from them. I am a paid scientific consultant for Novartis Vaccines and Diagnostics, Inc. A copy of my CV is enclosed.

2. I understand that the U.S. Patent and Trademark office has rejected claims in patemt application Serial No. 09/466,035 as obvious over the combination of Dubensky *et al.* (WO 95/07994; "Dubensky") and Hu *et al.* (AIDS Res. Hum. Retrovir. 7:615-620 (1991); "Hu").

3. It is my opinion that a person of ordinary skill in the art reading Dubensky and Hu would not have expected success extrapolating from Hu's prime-boost approach with Vaccinia virus to using an alphavirus prime followed by a protein boost.

4. It is my belief that the immune responses stimulated by RNA-based and DNA-based viruses cannot readily be compared. At the time of filing it was recognized in the art that interactions of different viral species with the immune system is not sufficiently similar to extrapolate from one species to another. Alphavirus vectors are RNA-based. Hu's vaccinia vector is DNA-based. Based upon the known replication differences of the viruses and their different effects upon cells, determined in *in vitro* studies, one skilled in the art would have assumed that host responses to RNA viruses versus DNA viruses would be different and therefore not comparable. While the underlying biological reasons for differences in the immune response remain largely unknown I am aware of recent data suggesting viral tropisms are one reason for the different responses. Alphavirus vectors exhibit tropism for CD11c-positive and CD11B-positive dendritic cells and macrophages. Vaccinia virus, in contrast, preferentially targets CD33-positive monocytes (Yu et al. Vaccine 2006; Sanchez-Puig et al., J. Virol. 2004).

5. The prime boost approach appears simple today and that simplicity suggests the approach would be broadly applicable across different viruses and proteins. But the complexities of the immune system and viral biology mean that the skilled artisan could not, at the time of filing, have expected success extrapolating from the results with Hu's DNA-based Vaccinia virus prime and boost approach to a RNA-based alphavirus prime and boost approach.

All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: ___02/20/2009_____ ____/William B. Klimstra/_____

William B. Klimstra